Discovery & Optimisation of Novel Agonists of GPR119:

17th RSC/SCI Medicinal Chemistry Symposium

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Outline of talk

• Introduction to target and start point
• Cyanopyridyl as a replacement for sulphone
• Improving solubility
• Seizure assay and a return to the sulphone…..
• A hERG beating methylene
• Summary and learning
GPR119 as a target for diabetes

- Class A GPCR (deorphanised)
- Expression reported in pancreas, gut, (brain)
- Targeting an Agonist


- Enhanced incretin (GLP-1) secretion and direct effect on pancreas
- ‘Oral GLP-1’ concept – combination opportunity with DPPIV inhibitors
When something is too good to be true....

hGPR119 pEC$_{50}$: 6.3 (42%)*
hERG IC$_{50}$: 2.5 μM
logD: 2.9

hGPR119 pEC$_{50}$: 7.6 (44%)
hERG IC$_{50}$: 16 μM
logD: 2.1

- Robust Glucose lowering
- But also in GPR119 knock-out mice.....
- Off target activity


* cAMP potency EC$_{50}$ with intrinsic activity (% effect) relative to 50 μM oleylethanol amide (OEA; endogenous ligand)
Plan B - A second series.....

No hERG and on target efficacy

A) Sulphone

\[
\text{pEC}_{50} = 7.2 \text{ (83\%)*} \\
\text{Sol} = 0.03 \mu\text{M [c]} \\
\text{logD} = 3.2 \\
\text{hERG} = >33 \mu\text{M}
\]

Potency in mouse similar

\[
\text{pEC}_{50} = 7.3 \text{ (99\%)}
\]

*\text{cAMP potency EC}_{50} \text{ with intrinsic activity (% effect) relative to 50 \mu M oleoylethanol amide (OEA; endogenous ligand)*}
Plan B - A second series.....

No hERG and on target efficacy

A) Sulphone

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>pEC\textsubscript{50}</td>
<td>7.2 (83%)</td>
<td>3x</td>
</tr>
<tr>
<td>Sol</td>
<td>0.03 \text{µM} [c]</td>
<td>1000x</td>
</tr>
<tr>
<td>logD</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>hERG</td>
<td>&gt;33 \text{µM}</td>
<td></td>
</tr>
</tbody>
</table>

Potency in mouse similar

| pEC\textsubscript{50} | 7.3 (99%) |

B) Pyridine

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>pEC\textsubscript{50}</td>
<td>6.2 (71%)</td>
<td>30x</td>
</tr>
<tr>
<td>Sol</td>
<td>23 \text{µM} [c]</td>
<td>3x</td>
</tr>
<tr>
<td>logD</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>hERG</td>
<td>&gt;33 \text{µM}</td>
<td></td>
</tr>
</tbody>
</table>

Pyridyl N acting as acceptor (but less optimal than SO\textsubscript{2}Me)

- Pharmacophoric elements are lipophile (often carbamate) and acceptor
- Struggled to move from neutrals and retain potency

Key issues to address: Solubility / Potency / logD / Boc group
A) Understanding the insolubility of the sulphone

- Molecules pack – end to end via sulphone – sulphone interactions
  And in ladder interactions

- Seen in 1/4 of sulphones in CSD

Sol

logD

0.03 µM [c]

3.2

End-End 18%

Ladder 18%

Both 23% ★

None 41%
B) Optimisation of pyridine

- Summary of pyridine SAR with lines of constant $p\text{EC}_{50}$-$\log D$
  Ligand Lipophilic Efficiency (LLE)
  Sized by intrinsic activity (10-155%)

- CN represents a breakthrough!

- 2-substitution $\downarrow$ potency
- 3-substitution $\uparrow$ potency
Bringing it all together

- Me adds potency (& logD)
- CN adds potency (& lowers logD)

<table>
<thead>
<tr>
<th>pEC$_{50}$</th>
<th>Sol (μM)</th>
<th>logD</th>
<th>LLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.2 (71%)</td>
<td>23 μM</td>
<td>3.4</td>
<td>2.8</td>
</tr>
<tr>
<td>6.7 (68%)</td>
<td>45 μM</td>
<td>3.8</td>
<td>2.9</td>
</tr>
</tbody>
</table>

- pEC$_{50}$: 7.7 (155%)
- Sol: 32 μM
- logD: 2.8
- LLE: 4.9

- pEC$_{50}$: 6.7 (68%)
- Sol: 45 μM
- logD: 3.8
- LLE: 2.9
Bringing it all together

- pEC$_{50}$: 6.2 (71%)
  - Sol: 23 µM
  - logD: 3.4
  - LLE: 2.8

- pEC$_{50}$: 7.7 (155%)
  - Sol: 32 µM
  - logD: 2.8
  - LLE: 4.9

- pEC$_{50}$: 6.7 (68%)
  - Sol: 45 µM
  - logD: 3.8
  - LLE: 2.9

- pEC$_{50}$: 8.2 (171%)
  - Sol: 21 µM
  - logD: 3.3
  - LLE: 4.9

- Me adds potency (& logD)
- CN adds potency (& lowers logD)

Key issues to address: Solubility / Potency / logD / Boc group

- 100x potency improvement
- LogD neutral
- Solubility maintained
Oxadiazole as an isostere for Boc

Key issues to address: **Solubility / Potency / logD / Boc group**

- Compound is active *in vivo* in wild-type **BUT NOT** knock-out mouse
- Glucose & GLP-1 endpoints
  
  On target efficacy
Improving Solubility #1 - An alternative to Boc.

Key issues to address: Solubility / Potency / logD / Boc group

Strong ether acceptor not satisfied by any H-bond donors
Improving Solubility #2 - Not all oxadiazoles are equal...

Acceptor scales - $\log K_b$


Subsequently shown to correlate with electrostatic potential by


Key issues to address: Solubility / Potency / logD / Boc group
Riding the line of LLE down to improve properties

Potency vs logD

Control of lipophilicity by oxadiazole isomer
Big impact in terms of solubility
Benefits in terms of hERG
Loss in potency offset by increased free levels

[MedChemCommun., 2013, 4, 95]
Problems seen in mouse toxicity studies

Clonic convulsions in 2 mice (day 10 @ 300mpk) whilst undergoing an IRWIN assessment

- **Seizure**: synchronized abnormal neuronal activity that **may** result in a number of behavioral symptoms including tonic-clonic convulsion

- **Convulsion**: the behavioral consequence of a seizure – typically muscle rigidity followed by rhythmic jerking movements
  - Convulsion ≠ seizure
  - Abnormal motor events, syncopal events, etc. may be incorrectly mistaken for convulsions

How can we find a back-up compound?
**In vitro Brain Slice**

- Evoked population spike: Summated firing of CA1 pyramidal neurones (measure of cell excitability and underlying synaptic activity)
- Potentially seizurogenic compounds can induce excitatory effect by variety of potential mechanisms


- Population spikes recorded from CA1 layer of hippocampus
  - Convulsant compounds (e.g. bicuculline) cause an increase in neuronal excitability which is reflected as:
    - Appearance of multiple population spikes
    - Increase in PS area (shaded grey)
    - Note that visible changes in PS shape usually precede quantifiable changes in PS area

| 0.1% DMSO | 10 μM bicuculline |
**In vitro Brain Slice**

- Evoked population spike: Summated firing of CA1 pyramidal neurones (measure of cell excitability and underlying synaptic activity)
- Potentially seizurogenic compounds can induce excitatory effect by variety of potential mechanisms


- Population spikes recorded from CA1 layer of hippocampus
  - Convulsant compounds (e.g. bicuculline) cause an increase in neuronal excitability which is reflected as:
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**Graphs:**
- Compound caused a concentration-dependent increase in excitability, consistent with a convulsant compound
Results from Brain Slice Assay

• Future compounds should not contain a CN pyridyl to avoid this issue
• Impact is that achieving high solubility will be challenging.....
• & compounds may have a hERG issue.....

Future chemical structures and their properties:

<table>
<thead>
<tr>
<th>Description</th>
<th>logD</th>
<th>pEC_{50}</th>
<th>Sol (µM)</th>
<th>hERG (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ve Brain slice</td>
<td>3.3</td>
<td>7.6</td>
<td>140</td>
<td>18</td>
</tr>
<tr>
<td>+ve Brain slice</td>
<td>2.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matched Pair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-ve Brain slice</td>
<td>4.0</td>
<td>7.6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>-ve Brain slice</td>
<td>3.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Circumventing hERG

hERG can be difficult to predict
- Structure driven rather than logD
- Small changes can have a big effect

‘Unlucky’ here – can we fix it?

86% of cpds > 10uM

\[
\text{\textbf{pEC}}_{50} \quad 7.6 \quad (121%) \\
\text{logD} \quad 3.0 \\
hERG \quad 7uM
\]
Circumventing hERG

hERG can be difficult to predict
- Structure driven rather than logD
- Small changes can have a big effect

‘Unlucky’ here – can we fix it?

CH$_2$ spacer to polar sulphone removes hERG liability (potency and logD neutral)

Oxadiazole isomer raises logD (increases potency & hERG)
Circumventing hERG

hERG can be difficult to predict
- Structure driven rather than logD
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'Unlucky' here – can we fix it?

CH₂ spacer to polar sulphone removes hERG liability (potency and logD neutral)

Oxadiazole isomer raises logD (increases potency & hERG)

Combination gives good potency & hERG
Further results from Brain Slice Assay

- CH$_2$sulphone also clean in brain slice assay

![](image)
Understanding the solubility of the CH₂ sulphone

- End to end interaction is absent
- Ladder interactions observed (Both α-CH interacting with O)

Solubility:
- [Sol] 1.8 μM
- logD 3.4
Overall Profile looks good

- Hu pEC\textsubscript{50} 8.1 (84%)
- Mu pEC\textsubscript{50} 7.2 (71%)
- logD 3.4
- LLE 4.7

Good Suspension PK (m,r,d) with dose linearity

- On-target, glucose lowering & GLP-1 release

Clean in Brain Slice assay
Synthesis – Oxadiazole isomers from N-CN

\[
\begin{align*}
\text{HN} & \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{R} \\
\text{CNBr, NaHCO}_3, \quad \text{CH}_2\text{Cl}_2/\text{H}_2\text{O}, \quad 59\% \\
\text{N} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{N} \quad \text{O} \quad \text{R} \\
\end{align*}
\]

\[\text{O} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{R}\]

i) \(\text{NH}_2\text{OH}.\text{HCl}, \text{Na}_2\text{CO}_3, \text{DMF};\)
ii) \((\text{XCO})_2\text{O}, \text{pyridine, toluene, } \Delta\)

\[\text{X} \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{R}\]

i) \(\text{X} \quad \text{C}=(\text{NOH})\text{NH}_2, \text{ZnCl}_2, \text{THF/EtOAc};\)
ii) \(\text{HCl, EtOH, } \Delta\)

\[\text{X} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{R}\]

i) \(\text{NaN}_3, \text{Et}_3\text{N.HCl, toluene, } \Delta;\)
ii) \(\text{(iPr)}_2\text{NEt, } (\text{XCO})_2\text{O}, \text{Chlorobenzene, } \Delta\)

- All 3 isomers available from common building block
- Chemistry works on phenol \((R=H)\) or with protection \((R=Bn)\)
Convergent synthesis of 10 steps. Longest linear sequence 6 steps Run on >100g scale

- CH₂SO₂Me building block introduced as last step
- NaSO₂Me displacement of bromo avoids need for S-oxidation
- Pd catalysed Br to OH conversion works in presence of heterocycle
Summary

![Chemical structures with properties]

- **pEC$_{50}$**: 7.2 (83%)
- **Sol**: 0.03 μM [c]
- **logD**: 3.2
- **hERG**: >33 μM

- **pEC$_{50}$**: 8.1 (199%)
- **Sol**: 7μM
- **logD**: 3.3
- **LLE**: 4.8

- **pEC$_{50}$**: 7.6 (220%)
- **Sol**: 120 μM
- **logD**: 2.7
- **LLE**: 4.9

- **pEC$_{50}$**: 8.1 (84%)
- **Sol**: 1.8μM
- **logD**: 3.4
- **hERG**: >33 μM

- **pEC$_{50}$**: 7.6 (121%)
- **Sol**: 1μM
- **logD**: 3.0
- **hERG**: 7μM
Conclusions & Learning

Startpoint
- Biggest difference to where you end up!
- Potency lead confidence that contradiction could be resolved
- Solubility lead

LLE
- pEC$_{50}$-logD
- good guide to progress (cpd quality)
- keeps phys props at the forefront
- Use with caution (agonists)

‘CH$_2$’
- a small group makes a big difference
- solved hERG

Oxadiazoles
- Not all bio-isosteres are equal!
- Subtle changes have big impact

X-ray structures
- Can really assist design teams
- “Beauty is truth, truth beauty”

Figure 2: “Hydrogen bond” scheme is displayed. No classical H-bonds are found but close C-H…O interactions exist between the sulfonyl groups.
Acknowledgements

Lead Generation (Mö)
Anders Broo
Öjvind Davidsson
Udo Bauer
Linda Sundström
Birgitta Svalstedt Karlsson
Walter Lindberg
Ann-Charlotte Egnell

Chemistry
Roger Butlin
Jamie Scott
Paul Schofield
David Clarke
Jules Hudson
Sam Groombridge
Kristen Goldberg
Alan Birch
Ruth Poulton
Sue Bowker

Phys / Comp Chem
Andrew Leach
Matt Wood
Phil MacFaul

Bioscience
Katy Brocklehurst
Carina Ämmälä
Joanne Teague
David Laber
David Baker
Rob Garcia
Simon Poucher
Steve Bloor

DMPK
Charles O’Donnell
Hayley Brown
Pablo Morentin Gutierrez
Teresa Collins

Project Leader
Darren McKerrecher

Large Scale Chemistry
Neil Hawkins
David Rudge
Pete McLachlan

Pharmaceutical Development
Claire Patterson

Statistics
Liz Mills

Legal
Tom Miller

Informatics
Jasen Chooramun

Animal Science & Welfare
Bill Brown
Neil Reavey
Diane Tibbs
Ruth Storer
Adrienne Sanders
Paul Sheridan
Lisa Shawcross
John Burton
Gary Slade
Laura Hayward

X-Ray
Per Svensson
Anne Ertan